UNITED STATES DEPARTMENT OF COMMERCE
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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/377,316	01/24/95	MURGITA R	06727/006001

GUSKER, S
EXAMINER

18N2/0404

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ART UNIT	PAPER NUMBER
1812	7

DATE MAILED: 04/04/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-24 are pending in the application.
   Of the above, claims 1-18 & 22-24 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 19-21 are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 1-24 are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-3, drawn to cell culture media, classified in Class 435, subclass 240.3.

Group II. Claims 4-11, drawn to methods to grow cells, classified in Class 435, subclass 240.2.

Group III. Claims 12-18, drawn to methods to inhibit myelotoxicity in a mammal, classified in Class 514, subclass 2.

Group IV. Claims 19-21, drawn to methods to promote proliferation in a mammal, classified in Class 514, subclass 2.

Group V. Claims 22-24, drawn to methods to prevent transplantation rejection, classified in Class 514, subclass 885.

The inventions are distinct, each from the other because of the following reasons:

Groups I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the cell culture media of Group I can be used as the starting material for the production and purification of

recombinant α-fetoprotein from host cells transfected with the nucleic acid for α-fetoprotein.

The culture media of Group I is materially distinct from, and is not used in or produced by the methods of Groups III-V.

Although there are no provisions under the section for "Relationship of Inventions" in MPEP 806.05 for "inventive groups that are directed to different methods; restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons:

Groups II-V (methods of growing cells, methods to inhibit myelotoxicity in a mammal, methods to promote proliferation in a mammal and methods to prevent transplantation rejection, respectively) are directed to methods that are distinct both physically and functionally, and are therefore patentably distinct, and are not required one for the other.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because the literature searches required for the two inventions are not co-extensive and therefore references that would anticipate one invention would not necessarily anticipate or even make obvious any of the other inventions, restriction for examination purposes as indicated is proper. Furthermore, there are different issues for the search and examination of each, which would also be unduly burdensome.

A provisional election was made by voice-mail message by Karen F. Lech on 2/9/96 without traverse to prosecute the invention of Group I, claims 19-21. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-18 and 22-24 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification does not provide any examples and insufficient guidance to enable the skilled artisan to administer human α-fetoprotein to a mammal in order to stimulate bone marrow cell proliferation because the only evidence provided in the specification for the biological activity of the human α-fetoprotein is increased thymidine incorporation by murine bone marrow cells in culture. This is not considered enabling for the

use of human α-fetoprotein in a mammal for the following reasons. It is not known if the desired biological properties of human α-fetoprotein can be retained if administered through any of the therapeutic routes postulated on pages 20-21 of the instant specification because of immunological reactions that would be initiated by the administration of a foreign protein to a mammal of any mammalian species. Further, an extrapolation from an in vitro tissue culture system to in vivo use cannot be made in this instance because human α-fetoprotein is not administered for any condition in the prior art, and Applicant's prophetic assertion of a dosage range of 10^{-10} to 10 g/kg body weight (page 21, lines 13-14) is mere speculation because it varies over 11 orders of magnitude (or a hundred billion fold!) and is therefore useless as guidance to the skilled artisan for dosage selection for a mammal. In addition, the pharmacological distribution and in vivo stability of human α-fetoprotein are not addressed in the specification, so Applicant's assertion of an oral, transdermal, or nasal transmucosal absorption of human α-fetoprotein is mere speculation because no examples or guidance is provided that would enable the skilled artisan to successfully administer the protein in a manner that would let a large protein molecule be absorbed without being denatured or hydrolyzed by endogenous peptidases. Likewise, the duration of treatment with human α-fetoprotein for a mammal is unknown and unpredictable because it

is not known if the newly-proliferated bone marrow cells would die upon cessation of treatment with the human α-fetoprotein. Therefore, the single example of increased thymidine incorporation by murine bone marrow cells in culture does not provide the skilled artisan with sufficient guidance to enable him to predict the successful dosage, duration of treatment, route of administration, or even if human α-fetoprotein would work in the desired manner due to antibodies raised against it as a foreign protein once administered in the body of a mammal for the reasons set forth above, and it would constitute undue experimentation for the skilled artisan to determine all of these factors in order to practice the invention as claimed. Finally, an abstract from the prior art co-authored by the Applicant indicates that human α-fetoprotein (AFP) can have suppressive effects on human bone marrow derived cells; "the inhibitory effect of AFP on PHA-induced lymphocyte proliferation was not altered by increases in mitogen dose...human AFP apparently effectively suppresses certain T cell-mediated reactions..." (Murgita et al., 1978, abstract). The instant situation is directly analogous to that which was addressed in In re Colianni, 195 USPQ 150, CAFC, which states that in the absence of examples, a method relying on a "sufficient" amount of therapeutic agent must disclose what the "sufficient" amount is and conditions associated with such. In the absence of such, a disclosure does

not meet the requirements of 35 U.S.C. 112 first paragraph. Furthermore, this information is crucial for practicing the invention as claimed because it was known in the art at the time the invention was made of the suppressive effects (anti-proliferative) on in vitro lymphocyte responses displayed by administering AFP, which runs counter to the intended use language of the claims which recite a method of promoting bone marrow cell proliferation. Again, In re Colianni noted that a "reference taught that indirect application of high doses of ultrasonic energy could lead to spontaneous bone fractures. Thus, the PTO provided sufficient evidence and reasoning to make a prima facie showing that appellant's disclosure was not commensurate in scope with the claimed invention (which requires mending of the fracture)".

Should the Applicant overcome this rejection, a rejection based on scope would be made over claim language reciting a "fragment or analog" of AFP. The disclosure provides insufficient examples or guidance to enable the skilled artisan to determine what would constitute a "fragment or analog" of AFP that retained its desired biological properties because the critical domains of the protein that bestow upon it its physiological function have not been identified or described. The disclosure is also silent as to what crucial amino acid residues are necessary and sufficient to provide a biological

function to any and all fragments or analogs of the instant AFP that can possibly be conceived or constructed. Absent sufficient examples or guidance, it would constitute undue experimentation for the skilled artisan to have to construct and test any and all of the virtually infinite number of possible fragments and analogs of AFP that the claims encompass, and no one fragment or analog would be predictive of all the others due to the well known unpredictability in the art of ascertaining a protein's function from its amino acid sequence.

2a. Claims 19-21 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

3. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

3a. Claims 19-21 are rejected under 35 U.S.C. § 103 as being unpatentable over Hoskin et al.

Hoskin et al. teach "that AFP selectively stimulates in vitro proliferation of two distinct subsets of adult murine bone marrow cells" (abstract). Hoskin et al. do not teach the in vivo administration of AFP to a mammal. It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer AFP to a mammal to promote bone marrow cell proliferation because one would expect that the results obtained with the murine bone marrow cells in vitro would be predictive of success in vivo, absent evidence to the contrary. The skilled artisan would be motivated to promote bone marrow cell proliferation to replenish cells lost due to various reasons, such as after chemotherapy for cancer in mammals.

It is noted that although claims 20 and 21 are methods claims, they recite product-by-process language. The process by which a product is produced for use in a method does not render the product or the method patentably distinct per se; the product is naive to its origin. Recombinant human AFP is not patentably distinct from isolated and purified human AFP, and unglycosylated human AFP is not patentably distinct from glycosylated human AFP due to the inherent properties of the primary, secondary, and tertiary structure of the amino acid

sequence itself, absent a showing by the Applicant to the contrary that a patentable distinction does exist.

4. No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (703) 308-6571. The examiner can normally be reached on Monday to Friday from 0800 to 1630.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Garnette Draper, can be reached on (703) 308-4232. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SG

Stephen Gucker

March 1, 1996

GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800